REMARKS

Claims 1, 3-18 and 20-36 were examined and rejected. Claims 13 and 28 have been amended. Claims 16 and 29 have been canceled without prejudice or disclaimer, their subject matter having been incorporated into claims 13 and 28 respectively.

As explained in the following section, all but one of the unelected, withdrawn claims are being replaced by new claims (57-72) so that they remain commensurate in scope with the elected product claims for later rejoinder.

All the amendments and new claims are supported by the original claims and throughout the specification. No new matter is added by these amendments. Entry and allowance of the amended and new claims is respectfully requested.

I. ELECTION OF CLAIMS AND REJOINDER OF UNELECTED CLAIMS

The Action acknowledges Applicants' election of claim 18,, 20-23, 28 ad 29 (Group VI) and restates the Examiner's agreement to rejoin claims 1, 3-6, and 13-17 (Group III) insofar as these are drawn to recombinant attenuated CB4-P virion with a heterologous polypeptide expressed as an N-terminal fusion of the viral polyprotein. The Office further considered and agreed to rejoin Groups II and V. As a result, claims 1, 3-18 and 20-36 are under examination, whereas claims 2, 19, and 37-53 are withdrawn from consideration. However, as discussed below, unelected process claims commensurate in scope to allowable product claims will be rejoined by the Examiner at the appropriate time.

The Action goes on to acknowledge Applicants' statement that allowance of virus or nucleic acid products would result in allowability of corresponding method groups. The Office notes that in accordance with MPEP § 821.04 and *In re Ochiai*, rejoinder of process claims that are commensurate in scope with allowed product claims will occur following finding that product claims are allowable. The Action reminds applicants of the necessity to amend process claims during examination to maintain (a) dependency from product claims or (b) inclusion of all limitations of product claims.

Applicants are therefore submitting new process claims 54-72 (that replace original process claims 37-51 and 53, and to add several "new" claims (rather than amending the original process

claims).[1] Applicants believe these new claims, both the replacements and several claims that don't correspond precisely to a canceled claim, are commensurate in scope with the product claims being examined. The Table set forth below lists the new claims, the original claims to which they correspond, and the product claims with which they share scope. Applicants respectfully urge the rejoinder or joinder of these claims upon determination of allowability of the product claims.

New Claim	Corresponds to original Claim:	Scope commensurate with product Claim:
54	37	1
55		3
56	38	1
57	40	1*
58	43	1
59		32
60	39	7
61	41	14
62	42	15
63	44	34
64	45	34
65	46	33
66	45	33
67	47	35
68	48	36
69	49/37	1
70	5037	1
71	51/37	1
72	53	15

* practically, if not literally commensurate

II. OBJECTION TO IMPROPER DEPENDENT FORM (under 37CFR 1.75(c))

Claims 16 and 29 were objected to. Claim 16, dependent from claim 13, recites "inserted directly **after** the first codon of the viral polyprotein" whereas claim 13 recites "inserted ... directly **upstream of sequences which encode VP4.**" (emphasis added). The language of claim 16 is said to contradict the language of claim 13 and therefore not limited it properly. Claims 28 and 29 are also asserted to bear the same deficiencies.

[1] Note that, without prejudice or disclaimer, Claim 52 is not being resubmitted in amended form at this time.

As Applicants understand it, the Office Action is saying "how can the nucleic acid that is directly upstream of VP4 sequences now be said to be inserted directly "after" the first codon of the viral polyprotein."

Applicants have amended claims 13 and 28 in the same way to indicate that, while the insert is upstream of the VP4 coding sequence (of the polyprotein), the option exists (formerly expressed in claims 16 and 29) to position the insert 3 nucleotides further in (*i.e.,* in the 3'-direction), after the Met codon that is the start signal of the viral polyprotein (which begins with VP4). This embodiment is clearly set forth in the specification, for example in the lower part of Figure 7 which shows the T-R-A-L-F-Q amino acid sequence situated after the initial M which is encoded by the CVB4 codon AUG (in genomic RNA; ATG in the cDNA clone illustrated) beginning at nt 744.

Applicants' intention to allow for such a one amino acid residue shift led to the claim draftsman's use of language that introduced an apparent contradiction between Claim 16 and its parent Claim 13. Because amended Claims 13 and 28 now include this embodiment, Claims 16 and 29 have been canceled.

It is believed that this amendment adequately addresses the Office's objection.

III. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner's Action rejected claim 17 as being indefinite for the reasons detailed below. Applicants respectfully submit that in light of the amendment and the following discussion, it would be appropriate to withdraw these grounds of rejection.

Claim 17 was rejected as indefinite because it recites "the insert is from about 60 nt to about 360 nt." The Office asserts that it is not clear whether the 60 and 360 refers to a "size" limitation or to a position within the CB4 sequence. Applicants believe that a person of ordinary skill in the art would have no confusion as to what is intended, namely, the length of the insert. Therefore, no amendment should be necessary.

Applicants have nevertheless amended the claim, for clarification only, but with no intention to alter its intended scope, to read: "...the length of insert is from about 60 to about 360 nucleotides. Note that the word "nucleotide" has been inserted in place of the abbreviation "nt" for purposes of clarity. In view of this amendment, the indefiniteness rejection may properly be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. § 102

The Office rejected the claims as anticipated under § 102(a) for the reasons detailed below. In light of the Ramsingh Declaration and the following discussion, it would be appropriate to withdraw these grounds of rejection.

A. Rejection under § 102(a) and Discussion:

1. Claims 1, 38 and 20-36 were said to be anticipated by Reference A, Halim *et al.*, *AIDS Res Hum Retroviruses 16*:1551-8 (2000)[2]

2. Claims 1, 3-1, 18, 20-27, and 30-36 were said to be anticipated by Reference B, Halim *et al.*, *Vaccine 19*:958-65 (2001)[3]

B. Applicants' Response

These two publications by the inventors' and their colleagues in part formed the basis for the present application. Submitted herewith is the Ramsingh Declaration, in accordance with *In re Katz*, 215 USPQ 14 (CCPA 1982), that states that the only inventors of subject matter in these publications are the named inventors, and that additional co-authors did not make any inventive contribution. Applicants do not believe that it is necessary to discuss here the substance of this rejection.

As the CCPA noted in its decision in *Katz*, unlike the filing of a patent application, the publication of an article is not deemed a constructive reduction to practice of the subject matter described therein, citing *In re Schlittler*, 110 USPQ 304, 305-306 (CCPA 1956). The Court in *Katz* specifically ruled that "authorship of an article by itself does not raise a presumption of inventorship..." Accordingly, the Court noted that disclosure in a publication does not prove that any "invention" (within the meaning of § 102(g)) has ever been made by anyone. Similar logic should apply with respect to inventions of **another** under §102(a).

As explained in the *Katz* opinion, it would be incumbent upon Applicants "to provide a satisfactory showing which would lead to a reasonable conclusion that he is the sole inventor."

In this case, co-inventor Ramsingh has signed a declaration that she and co-inventor Halim are the only inventors of the claimed invention. Since, according to the *Katz* decision, all that "is required is a reasonable showing supporting the basis for the applicant's position." Applicants

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[2] Full cite: Halim SS, Collins DN and Ramsingh AI., "A therapeutic HIV vaccine using coxsackie-HIV recombinants: a possible new strategy." *AIDS Research and Human Retroviruses 16(15)*:1551-1558 (2000 Oct. 10)

[3] Full cite: Halim SS, Ostrowski SE, Lee WT, Ramsingh AI., "Immunogenicity of a foreign peptide expressed within a capsid protein of an attenuated coxsackievirus," *Vaccine 19(7-8)*:958-65 (2001 Nov 22)

believe that they have made such a showing. Since Reference A and Reference B are not evidence of invention ***by another*** under § 102(a), but rather, describe the invention invented by the present named inventors that is claimed herein, these references are unavailable as citeable prior art against the present claims. It would therefore be proper to withdraw the §102(a) rejection.

V. REJECTIONS UNDER 35 U.S.C. § 103(a)

The Office Action has rejected claims 1, 3-6, 13-18, 20-23,, 28 and 29 as being obvious over Tracy *et al.*, WO 98/39426 (**"Tracy"**). For the reasons detailed below, Applicants respectfully submit that it would be appropriate to withdraw this ground of rejection.

A. Legal Test for Nonobviousness:

The burden of establishing a case of *prima facie* obviousness rests with the Patent and Trademark Office. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Moreover, an obviousness rejection "must be based on *evidence* (statutory prior art, admissions against interest)... ." *In re McKellin*, 188 USPQ 428, 432 (CCPA 1976), emphasis in original. The Federal Circuit Court of Appeals has repeatedly articulated the requirements of a proper analysis:

> [W]here claimed subject matter has been rejected as obvious in view of ... prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co., ...* 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced because, as will be discussed below, the cited art does not suggest that the methods claimed be carried out **with a reasonable expectation of success.**

B. Specific Rejection

According to the Office Action, Tracy allegedly discloses

> [C]oxsackie virus B serotypes 1-6 and attenuated coxsackievirus vectors for delivery of nucleic acids encoding antigenic or therapeutic products, where heterologous nucleic acids may be inserted, for example between a coding sequence for a capsid protein and coding sequence of viral protease, or at the start of the genome's open reading frame or at other locations."

Importantly, as discussed below, Tracy describes results only with coxsackie virus B3 (CVB3). However, according to the Examiner, because Tracy discloses high level of organizational similarity among coxsackieviruses,

> any of the coxsackievirus B serotypes or other coxsackieviruses can be attenuated and modified for use as expression vectors for heterologous nucleic acids **in the same manner as otherwise taught by Tracy *et al.***

emphasis added. This led the Office to conclude that it would have been obvious to make a recombinant attenuated CVB4 with an inserted heterologous nucleic acid, including an insert at the start of the sequence that encodes VP4. This conclusion by the Office requires the conclusion that the "high level or organizational similarity" among the coxsackievirus serotypes would create an **expectation** that one could similarly genetically manipulate any CVB and obtain an equivalent expression vector that could (1) be used to express the heterologous polypeptide and (2) be used successfully (which includes **safely)** as an immunogenic vector *in vivo*.

C. Applicants' Response

Applicants disagree with the Office's understanding of the prior art as exemplified by Tracy. While correct in its reading of Tracy that viruses of the coxsackievirus B (CVB) serotype share a great deal of organizational similarity, the Office has failed to appreciate a central fact that lies at the heart of the differences among these viruses, particularly as it applies to the present invention. For reasons discussed below, it should be evident that one cannot predict from what has been found for other CVB's whether a particular mutational event, such as inserting a heterologous nucleic acid sequence encoding an antigenic epitope as is done in the present invention, alongside or into a viral protein gene, will result in a gain or loss of pathogenicity/virulence by the resulting vector virions. For use in accordance with the present invention, it is important that the vector not be a pathogen in the species in which it is being used (*i.e.,* **loss, but not gain**, of virulence/pathogenicity may be acceptable). Thus the present rejection fails, at least on the "expectation of success" test, to support a *prima facie* obviousness rejection.

It is well known that in designing CVBs as expression vectors, it is crucial to understand what sequences in the virus are responsible for causing disease. This is because, if the vector is pathogenic, then it is no longer useful as an expression vector intended to serve as an immunogenic composition *in vivo*. Although the basic genetic organization of the CVBs is similar, as the

Examiner gathered from the Tracy, the molecular determinants of virulence are very different depending not just on serotype but also on strain. Tracy's group (J.J. Dunn *et al.*, *J. Virol. 74*:4787-4794 (2000); "Dunn") and Huber's group (K.U. Knowlton *et al.*, *J. Virol. 70*:7811-7818 (1996)[4]; "Knowlton") have identified the virulence determinants for CVB3 whereas co-inventor Ramsingh's lab has done so for CVB4 (M. Caggana *et al.*, *J. Virol. 67*:4797-4803 (1993)[5]; "Caggana"). These are discussed below in more detail.

For the Examiner's convenience, Applicants wish to remind the Examiner of some basic facets of CVB3 viral genome structure. The single open reading frame, flanked 5' and 3' by nontranslated regions (NTRs) (referred to in the specification as "untranslated" or "UTRs") is subdivided into three regions, P1 to P3, that encode a polyprotein of 2,185 amino acids (aa). The P1 region encodes the viral capsid proteins VP1 (281 aa), VP2 (263 aa), VP3 (238 aa), and VP4 (69 aa). The P2 and P3 regions encode non-structural viral proteins important for polyprotein processing and nucleic acid replication and translation.

Knowlton notes at page 7816, left column, that CVB3 virulence can be attenuated by a mutation in an external loop of VP2. The 5'NTR of CVB3 also plays an important role in CVB3-induced cardiomyopathy. A mutation at nt 234 in the 5'NTR alters the myocarditic activity of the virus, even though the virus still replicates in the murine heart. Thus, even viral replication is not an adequate surrogate for actual testing of virulence or pathogenicity *per se*. These earlier-described mutations differed from those examined in the Knowlton study. Knowlton compared the full sequences of H3 and H310A1 (an antibody-escape mutant virus) and identified a single nonconserved mutation (A to G) in the P1 polyprotein coding region at nucleotide 1442 resulting in an Asn-to-Asp mutation in amino acid 165 of VP2. When nt 1442 of the H3 and H310A1 cDNA copies of the viral genome was mutated to change amino acid 165 of VP2 to Asp and Asn, respectively, the investigators found that Asn is associated with the myocarditic phenotype, while an Asp at the same site reduces the myocarditic potential of the virus. The mechanism underlying this change may have been related to induction of host defenses resulting in inflammation, because high-level production of tumor necrosis factor-α (a host defense mechanism, turned pathogenic) by

[4] Copy of Dunn and of Knowlton references submitted herewith as Exhibit A.

infected mouse monocytes was associated with Asn at that position residue VP2 position 165 (the pathogenic form). Knowlton emphasized the potentially important differences between this H3 variant of CVB3 and other previously published CVB3 variant, concluding that "this suggests that multiple mechanisms may be important in the stimulation of an immune response and generation of a myocarditic phenotype." (page 7816 at column 2,line 6).

As described in Dunn (see abstract and page 4787- 4788 (left column), the viral capsid of coxsackieviruses contains determinants contributing to the pathogenic phenotype of CVB4 (citing Caggana, *supra*, and another paper by co-inventor Ramsingh), CVB3 (citing Knowlton, *supra*), and related polioviruses (PVs). In support of Applicants' position, it is important to note that **the sites determining the virulence phenotypes of these viruses do not colocalize to a single capsid region or even a sin0gle capsid protein,** further supporting the lack of an expectation of success of the present invention based on Tracy Virulence determinants are found in **all four** capsid proteins and are not necessarily located at surface-exposed residues of the virion. The results of Knowlton regarding Asp vs Asn at position 165 of VP2 were discussed further. Moreover, specific nucleotide(s) within the 5'NTR are also known to alter the virulence phenotype of CVB1 and CVB3. In the CVB3 5'UTR, a U→C mutation at nt 234 attenuates the cardiovirulence phenotype. Replacement of the cardiovirulent CVB3/M or CVB3/CO 5'NTRs with that from CVB3/0 attenuates the resultant viruses for myocarditis. Subsequent analysis of multiple clinical CVB3 isolates as well as other enteroviruses demonstrated that nt 234 is always U regardless of the cardiovirulence phenotype, consistent with 234C being an "artificial" mutation. ~~Zhang et al. (53) isolated~~ Another attenuated CVB3 strain (p14V1) resulted from passage of cardiovirulent CVB3/Nancy in human fibroblasts; the 5'NTR had a single nt change at position 690 (A→U). Insertion of 690U into the cardiovirulent parental virus did not alter the myocarditic phenotype, demonstrating that this mutation does not affect the cardiovirulence phenotype. Comparison of the 5'NTR and capsid coding region of this revertant to the attenuated p14V1 and cardiovirulent CVB3/Nancy strains suggested that amino acid 155 in VP1 might play a role in attenuation.

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[5] which is also cited in the specification, , at page 6 line 11 and 26; page 58, line 11; page 59, line 6, page 60, line 5; Page 62, line 19 and 27; page 65 lines 20 and 33; page 67, line 8; page 68 line 33; page 70, lines 24-30; page 76, line 13.

Prior to the Dunn publication, studies of genomic determinants of virulence for CVB3 and the majority of enteroviruses relied on strains engineered by physiochemical or biologic means in the lab. Dunn set out to examine the natural genetics of cardiovirulence in clinical CVB3 strains using two phenotypically and genotypically distinct CVB3 clinical isolates. The authors obtained the 5'NTR and P1 coding regions from CVB3/AS ("AS") and CVB3/CO ("CO") RNAs, constructed six intratypic chimeric viral genomes in the CO background, and tested the hypothesis that these genomic regions encoded determinants of the viral cardiovirulent phenotype. Upon testing *in vivo* for cardiovirulence, the authors found that replacement of the CO capsid coding region by that from the homologous region of CO did not change the CO phenotype. However, a recombinant virus containing the CO 5'NTR alone or the 5'NTR+capsid sequences together were not myocarditic, and infectious virus was not recoverable. Chimeric viruses containing the AS 5'NTR alone, capsid sequence alone, or both together preserved the myocarditic phenotype. The authors concluded that the 5'NTR is the primary site determining natural cardiovirulence.

In the CVB4 virus, a Met residue at position 129 of VP1 was shown to be an attenuating determinant while a Thr residue at the same position was shown to be a major determinant of virulence (Caggana, *supra*; specification at page 59, first paragraph). It was also shown in the specification (paragraph bridging pages 62-63) that disruption of the DE loop by the insertion of a heterologous sequence did not affect (induce) pathogenicity. Furthermore, CB4-P/HIV chimeric viruses CB4-P/HIV9_{104}, CB4-P/HIV9_{148}, and CB4-P/HIV10_{74}, which contained the HIV inserts retained their inserts after six passages in cell culture (Figure 8). In addition, the three chimeric viruses were genetically stable after passage *in vivo*. Pathogenicity testing showed that the recombinants retained the avirulent phenotype of the parental CB4-P variant. (paragraph bridging pages 69-70). The specification summarizes a number of findings in the paragraph bridging pages 78 and 79, where it states that

> ...insertion of foreign sequences within the genome of CB4-P does not alter the physical stability of the recombinants. In addition, expression of a short peptide within the VP1 capsid does not alter the ability of the recombinant to replicate in cell culture or in mice. However, expression of longer sequences at the amino-terminus of the polyprotein results in decreased replication both *in vitro* and *in vivo* and correlates with diminished pathogenicity. The CB4-P/HIV recombinants retain the biological and physical properties of the attenuated CB4-P variant, which appears uniquely suited as a viral vector for a therapeutic HIV vaccine.

Applicants assert, and are supported by the Dunn and Knowlton papers, that none of their observations with respect to the lack of pathogenicity of the genetically modified CVB4

recombinants of the present invention would have been known, evident or predicted from the disclosure of Tracy cited by the Office.

The studies performed by the present inventors in devising the claimed invention and the information that they have so gathered for CVB4 permitted them to design useful immunogenic vectors that they claim herein. These vectors express a desired heterologous polypeptide and at the same time, lack pathogenicity/virulence characteristic of wild-type CVB4 viruses. Because the information disclosed in Tracy would not have been directly applicable to a CVB of another serotype or strain, without first having carried out the appropriate investigation, at most there may have been a **wish** to insert a heterologous sequence into CVB4 for subsequent expression. In fact, though, there was no expectation of success. Thus, at most, the reference cited by the Office would support a conclusion of "obvious to try" which is not the standard for a *prima facie* obviousness rejection (*In re Tomlinson,* 150 USPQ 623 (1966)). Indeed, the Court of Appeals for the Federal Circuit and its predecessor, the Court of Customs and Patent Appeals have repeatedly and emphatically rejected such "obvious to try" rejections by the Patent Office as an improper test for obviousness under § 103. *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987); *N.V. Akzo v. E.I. DuPont de Nemours & Co.*, 810 F.2d 1148, 1157 (Fed. Cir. 1987) ("Of course, an 'obvious to try' standard is not a legitimate test of patentability"); *In re Yates*, 663 F.2d 1054, 1057 (C.C.P.A. 1481); *In re Goodwin*, 576 F.2d 375, 377 (C.C.P.A., 1978) (This court has consistently refused to recognize 'obvious to try' rejections").

In view of the foregoing discussion, because the Office has not met its burden for a *prima facie* obviousness rejection, it would be proper to withdraw the pending §103(a) rejection, and the Examiner is respectfully requested to do so.

VI. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims meet the requirements of 35 U.S.C. §112, second paragraph, are free of the prior art of record, and are therefore in condition for allowance. Applicants respectfully request early notice of such favorable action.

Examiner Wortman is respectfully requested to contact the undersigned at (202) 216-8584 with any questions or comments if they will assist in the understanding this amendment and response.

In the unlikely event that the Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to **Deposit Account 22-0261**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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